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Attorney Docket No. 13716
2058-181**REMARKS****I. Status Of The Claims.**

Claims 1-15, 18, 20-25, 27, 29, and 32-34 are pending in the Application. This Response and Amendment cancels Claim 3 and 14, and amend Claims 1, 9-12, 18, 20, 27, and 29.

II. Claim Amendments And New Claims.

The claim amendments and new claims are described below. Applicants respectfully submit that these claim amendments and new claims do not add new matter. Entry of the claim amendments and new claims is respectfully requested.

A. Claims 1, 12, 20, 27, and 29.

Claims 1, 12, 20, 27 and 29 have been amended to incorporate the definition of "X" from now cancelled Claims 3 and 14. Accordingly these amendments do not add new matter.

B. Claims 9-11 and 18.

The amendments to Claims 9-11 and 18 do not add new matter. Claims 9-11 and 18 are updated to reflect the amendments to Claim 1 filed in the previous paper, from which Claims 9-11 and 18 depend. Accordingly these amendments do not add new matter.

III. The Claimed Invention.

The invention is directed to a method for attaching biological molecules to a solid support in a two-step process. The present invention solves the problems of the prior art, which generally requires more than two steps, by requiring the combination of a solid support with an available amino group, and an activating group, which attaches both the solid support and the biological molecule. The advantages of the claimed invention over the prior art are that it is more efficient, economical, simpler and faster, with greater sensitivity.

For example, the present invention solves problems of the prior art, the acyl fluoride ("AcF") method of attachment disclosed in Milton, U.S. No. 6,143,833 by reducing the number of steps necessary to covalently attach a biological molecule to a solid support, and increasing the loading of biological molecules onto the solid support for synthesis and analyte detection. (*See, e.g., Specification, page 1*).

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2058-181**IV. The 35 USC § 112 Rejections.**

The Office has rejected Claims 9-11 and 18 under 35 U.S.C. § 112, first paragraph for the reasons stated in numbered paragraph 3 of the Office Action, and rejected Claim 18 under 35 U.S.C. § 112, second paragraph for the reasons stated in numbered paragraph 4 of the Office Action. The amendments to Claims 9-11 and 18 are believed to obviate this basis for rejection. Accordingly, withdrawal of the rejections is respectfully requested.

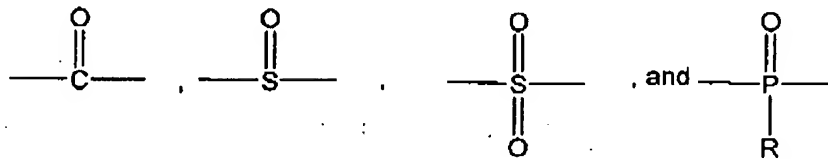
V. The 35 USC § 102 Rejection.

The Office has rejected Claims 1-2, 9, 11, 18, 20, 21, 27 and 33 under 35 U.S.C. § 102(b) as being anticipated by Hammen (U.S. Pat. No. 5,240,602) for the reasons stated in numbered paragraph 5 of the Office Action.

Independent Claims 1, 20, and 27 are limited to an activating compound, the activating compound having the structure:



wherein L_1 and L_2 are leaving groups, and X is selected from the group consisting of:



wherein

R is selected from the group consisting of alkyl, aryl, and OR^1 ;

R^1 is selected from the group consisting of alkyl and aryl; and wherein

the alkyl and aryl groups have having no greater than about 18 carbon atoms;

The claimed activating compound is not described in Hammen. Accordingly, Applicants request withdrawal of the Rejection under 35 U.S.C. § 102(b) on this basis.

VI. The 35 USC § 103 Rejections.**A. The Invention Is Non-Obvious Over Hammen, Hearn, and Stolowitz.**

Claims 1-4, 9-11, 18, 20-21, 25, 27, 29 and 33 are rejected under 35 U.S.C. § 103(a) as unpatentable over Hammen (U.S. Patent No. 5,240,602) and Hearn ("Methods in Enzymology", 1987, Vol 135, pp. 102-117) and Stolowitz et al. (WO 87/06586) for the reasons stated in numbered paragraph 8 of the Office Action.

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Applicants respectfully traverse these rejection on the basis that (1) the Office has not established a *prima facie* case of obviousness; and (2) The references teach away from the combination. Applicants respectfully request withdrawal of the rejection and allowance of all pending claims on the following basis.

Hammen does not disclose applicants' claimed activating compound, where X represents one of -C(=O)-, -S(=O)-, -S(=O)₂-, or -P(R)(=O)-. The Office seeks to remedy the deficiencies of Hammen by combining with the teachings of Hearn and Stolowitz et al., stating that "The combined references of Hearn and Stolowitz et al. (see entire document) teach, for example, -C(=O)- (e.g. see Hearn, abstract wherein CDI contains the requisite carbonyl); SEE ALSO Stolowitz et al., abstract, "The invention relates to the functionalization of particulate bonded phase chromatographic supports prepared by silanization of silica gel or controlled pore glass and containing pendant primary alkyl amine groups." Office Action, page 8.

Applicants respectfully submit that the Office has not provided a suggestion or motivation to combine the references and request withdrawal of the rejection on this basis.

1. There is no Suggestion or Motivation to Modify or Combine Hammen with Hearn.

To arrive at Applicants invention, the polymeric amine derivatized supports, cited by the Office in Hammen, must be combined with the activating compounds described in Hearn. The Office has not provided a suggestion or motivation to make such a combination and there is no teaching or suggestion in Hearn or Hammen of the desirability of the combination. For example, Hearn's disclosure of activation of hydroxyl derivatized supports does not teach or suggest Applicants' claimed invention which activates amine derivatized supports. Accordingly, the Office has not established a *prima facie* case for the combination of Hammen with Hearn.

2. There is no Suggestion or Motivation to Modify or Combine Hammen with Stolowitz.

To arrive at Applicants invention, the polymeric amine derivatized supports, cited by the Office in Hammen, must be combined with an activating compound described in Stolowitz. Further, the Office must provide a suggestion or motivation to make such a combination. The

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Office has not provided this suggestion or motivation.

As stated by the Office, the invention of Stolowitz "relates to the functionalization of particulate bonded phase chromatographic supports prepared by silanization of silica gel or controlled pore glass." No where in the Office Action does the Examiner provide a suggestion or motivation to combine the polymeric amine derivitized support disclosed in Hamman with the activating compound described in Stolowitz. Instead, the Office merely asserts that Stolowitz teaches the deficient limitations of Hamman and details the functionalization reaction.. See, Office Action page 8, par 5. Further, neither Stolowitz nor Hamman suggest the desirability of modifying the silica gel or controlled pore glass as described in Stolowitz, and using an amine derivitized organic polymer as the solid support with an activating reagent as claimed by Applicants. Accordingly, the Office has not established a *prima facie* case for the combination of Hamman with Stolowitz.

3. Stolowitz teaches away from Applicants' Invention.

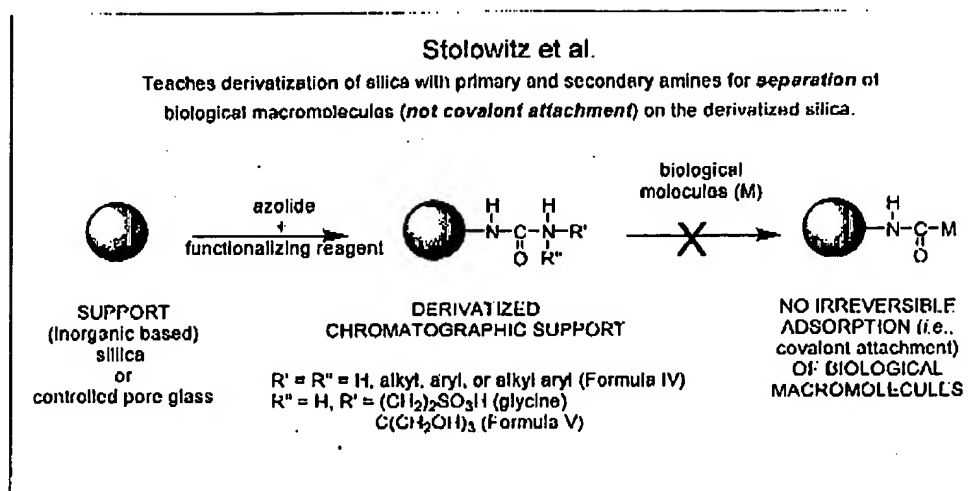
As detailed above, Applicants do not admit that the Office has established a *prima facie* case of obviousness. However, even if a *prima facie* case of obviousness has been established, it is rebutted by a teaching away from Applicants' claimed invention.

Each of the independent Claims is limited to a "biological molecule being a macromolecule" and "reacting the biological molecule with the activated support, thereby displacing L₂ and covalently attaching the biological molecule to the solid support." (emphasis added), in varying language. These limitations are expressly taught away from in Stolowitz et al.

Stolowitz et al. teaches away from the claimed invention by teaching *separation* of the claimed biological molecules, and expressly teaching against covalent attachment of the claimed biological molecules. Stolowitz et al. teaches derivitized silica and porous glass beads for chromatographic *separation* of biological macromolecules and low molecular weight amines (*i.e.*, biomolecules). As known to those of skill in the art and taught on page 2, lines 1-13; and page 4, lines 1-9 of Stolowitz, for the chromatographic support to suitably function, it is desirable that the chromatographic support does not irreversibly absorb (*i.e.*, covalently attach) the biomolecules. The teachings of Stolowitz et al. are illustrated in the figure below.

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Stolowitz teaches that the invention “**eliminates the adsorption of biological macromolecules and low molecular weight amines observed with bonded phase supports which are not further derivatized.**” (Stolowitz, page 4, lines 6-9, emphasis added). Thus, the invention described in Stolowitz precisely teaches away from that which Applicants claim, namely attaching biological macromolecules (e.g., oligonucleotides, nucleic acids, polypeptides, and carbohydrates) to a solid support. This is admitted by the Office in stating that Stolowitz teaches “The derivatization of the physical barrier preventing interaction between the hydrophobic silane backbone and sample components; . . .” Office Action page 11, lines 1-2, emphasis in original.

Attaching the claimed biological macromolecules, such as an oligonucleotide, is directly against the teachings of Stolowitz et al., which expressly teaches no irreversible adsorption (i.e., covalent attachment) of these molecules.

B. The Invention Is Non-Obvious Over Hammen, Hearn, Stolowitz, Milton, Okamoto, and Guo.

Claims 1-15, 18, 20-25, 27, 29 and 32-34 are rejected under 35 U.S.C. § 103(a) as unpatentable over Hammen (U.S. Patent No. 5,240,602) and Hearn (“Methods in Enzymology”, 1987, Vol 135, pages 102-117) and Stolowitz et al. (WO 87/06586) and Milton (US 6,146,833), Okamoto et al. (US 6,476,215) and Guo et al. (Nuc. Acids Res. 1994, pp. 5456-5465) for the

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reasons stated in numbered paragraph 9 of the Office Action. Applicants respectfully traverse this rejection on the basis that (1) the Office has not established a *prima facie* case of obviousness; and (2) The references teach away from the combination.

1. The Office Has Not Established A Prima Facie Case Of Obviousness Further Over Milton, Okamoto, and Guo For Claims 12-13, 15 and 32.

Independent Claims 1, 12, 20, 27 and 29 and the claims depending from these independent claims are non-obvious over Hammen, Hearn and Stolowitz for the reasons stated in paragraphs VI(A)(1-3) above. Claims 12-13, 15, and 32 are further limited to a solid support comprised of an organic polymer having at least one available amino group, the solid support selected from the group consisting of a plate and a film, in varying language. Plates and films are not disclosed in Hammen, Hearn, or Stolowitz and the Office looks to Milton et al., Okamoto et al., and Guo et al. to remedy the deficiencies of Hammen, Hearn, and Stolowitz. (Office Action, pages 9-12). Applicants respectfully submit that the Office has not further established a *prima facie* case of obviousness with respect to Claims 12-13, 15 and 32 and request withdrawal of the rejection on this basis.

(a) The Office Has Not Established A Prima Facie Case Of Obviousness Further Over Okamoto and Guo.

The Office has not provided a motivation to combine Hammen, Hearn, and Stolowitz with Okamoto et al., and Guo et al. as required to establish a *prima facie* case of obviousness with regard to Claims 12-13, 15 and 32. See, Office Action page 13, line 19, through page 14, line 3). Further, Applicants submit that the references themselves do not provide the requisite motivation to modify or combine the references to arrive at Applicants invention. Okamoto et al., and Guo et al., disclose glass or silica plates as substrates, and not an "organic polymer having at least one available amino group", as claimed by Applicants. In addition, these references do not disclose Applicants' claimed activating group. There is no motivation to modify or combine Okamoto and Guo with Hammen, Hearn and Stolowitz as neither Okamoto nor Guo teach or suggest an organic polymers as a substrate, or Applicants claimed activating group. Hammen, Hearn and Stolowitz also do not teach or suggest the combination as none of

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these references teach or suggest an amine derivatized plate or film.

(b) The Office Has Not Established A Prima Facie Case Of Obviousness Further Over Milton.

The Office has not provided a motivation to combine Hammen, Hearn, and Stolowitz with Milton, as required to establish a *prima facie* case of obviousness with regard to Claims 12-13, 15 and 32. See, Office Action page 13, line 19, through page 14, line 3). Further, Applicants submit that the references themselves do not provide the requisite motivation to modify or combine the references to arrive at Applicants' invention. Initially, Applicants would like to point out that the procedure for immobilizing biopolymers disclosed in Milton is a three-step process (*i.e.*, (1) derivatizing the aminated substrate to a carboxylated substrate; (2) treating the carboxylated substrate to form an acyl fluoride functionality; and (3) reacting the acyl fluoride functionality on the substrate with a biopolymer). In contrast, Applicants' claimed method is a two-step process where an activating compound is reacted with both an amino group on a solid support and a biological molecule.

Milton teaches immobilizing biopolymers on solid supports having acyl fluoride functionalities. As described throughout Milton, and shown in the scheme in Cols. 17-19 of Milton, aminated polypropylene is disclosed, among a myriad of other polymeric materials, as a starting material that is derivatized to have carboxyl functionalities. The carboxyl functionalities are then treated with a suitable reagent for forming an acyl fluoride functionality. The acyl fluoride functionality is then reacted with an amino derivatized biopolymer.

There is no teaching or suggestion in Milton of combining the aminated film with an activating compound as claimed by Applicants. Further, following the teachings of Milton, and combining Milton with the teachings of Hearn, results in a substrate having an acyl fluoride functionality, not Applicants' claimed "organic polymer having at least one available amino group". Reacting an acyl fluoride with the CDI described in Hearn, or another of Applicants' claimed activating compounds, would not result in attachment of the activating compound and subsequent attachment of the biological molecule. Both the acyl fluoride and the CDI are acyl compounds which typically undergo nucleophilic substitution and neither of these compounds is

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reactive as a base (i.e., a nucleophile). Accordingly, the modification changes the principle of operation of the references, i.e., the proposed combination would not immobilize a biopolymer, and there is no suggestion or motivation to modify the references. Applicants request withdrawal of the rejection and allowance of all pending claims, Claims 1-15, 18, 20-25, 27, 29, and 32-34 on this basis.

2. Milton Teaches Away From Applicants Invention.

As detailed above, Applicants do not admit that the Office has established a *prima facie* case of obviousness. However, even if a *prima facie* case of obviousness has been established, it is rebutted by a teaching away from Applicants' claimed invention.

Each of the independent Claims is limited to a "a solid support comprised of an organic polymer having at least one available amino group" and "reacting the available amino group on the solid support with an activating compound, the activating compound having the structure: L₁ - X - L₂" These limitations are expressly taught away from in Milton and under USPTO practice and procedure, the references must be considered in their entirety. MPEP § 2141.02. Applicants request withdrawal of the rejection and allowance of all claims based on the following teachings of Milton.

Initially Applicants would like to point out that Milton teaches the general unsuitability of covalent attachment of biomolecules, such as an oligonucleotide, using Applicants claimed activating compounds, such as a carbodiimide. For example, col. 1, lines 43-56 states:

presynthesized or natural oligonucleotides have been immobilized by covalently attaching activated oligonucleotides to the solid support. Typically, this approach requires activating the oligonucleotide with e.g., a carbodiimide. Unfortunately, the activated oligonucleotides are expensive and they have short useful lives because they are very unstable. Thus, preparing and utilizing these activated oligonucleotides often lead[s] to the loss of expensive reagents when the activated oligonucleotide decays to an inactive form. Moreover, carbodiimide activation frequently results in urea side product formation. Since these ureas tend to be insoluble in many common organic solvents their presence in automated reaction systems can cause problems when tubing and other lines are clogged by the precipitate.

Next, Milton as a whole teaches the unsuitability of plates and films for attaching

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biopolymers. For example, Milton states:

[G]lass slides, silicon wafers and polymer films are difficult to handle, and require handles or specially designed holders in order to manipulate the solid support Furthermore, it is difficult to characterize and control the surface density of biopolymers synthesized or attached to glass slides and polypropylene films. Thus, there is a continuing need for improved material suitable for immobilizing biopolymers. (Milton, col. 2, lines 5-27).

Milton then teaches that solid supports fabricated with acyl fluoride functionalities overcome the disadvantages of the prior art. (Milton, col. 3, lines 53-66).

Milton teaches aminated polymers for use as a starting material and only in the context of further derivatizing the aminated polymers to form an acyl fluoride functionality. Further, Milton teaches away from the combination with Hearn and Stolowitz by teaching that underivatized aminated sites on the starting polymer should be *blocked* prior to reaction with a biopolymer. (Milton, col. 17, line 9, through col. 18, line 2). It is improper to combine references where the references teach away from their combination. MPEP § 2145(X)(D)(2). Accordingly, there is no suggestion in Milton that "an organic polymer having at least one amino group" is desirable for reacting with Applicants claimed activating compound and attaching a biological molecule.

Accordingly, one of skill in the art, considering Milton in its entirety, would not be motivated to select an aminated polypropylene, and combine it with an activating compound, such as those cited by the Examiner in Hammen, Hearn, and Stolowitz, as Milton describes the unsuitability of such a covalent attachment. Applicants request that the Office consider all the teachings of Milton, withdraw the rejection and allow all pending claims, Claims 1-15, 18, 20-25, 27, 29, and 32-34.

C. Applicant's Invention Exhibits Significant And Unexpected Results Over The Prior Art.

Applicants submit that, insofar as the claims may be *prima facie* obvious (which is denied), any such *prima facie* case is rebutted by the evidence of the superior and unexpected results of Applicants' claimed method for attaching a biological molecule.

It is well-settled law that a *prima facie* case of obviousness under 35 U.S.C. § 103 can be rebutted by evidence that the claimed invention provides unexpected advantages, and that

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evidence provided by the specification itself must be considered. The experimental results set out in the specification provide evidence that the claimed invention provides unexpected advantages for attaching a biological molecule. In particular, the test results summarized in Examples 2 and 3 of the Specification are evidence of the remarkable ability of the claimed invention to attach a biological molecule, exhibiting increased oligonucleotide loading and higher sensitivity for analyte detection than prior art acyl fluoride (AcF) method, an example of the method disclosed in Milton, and CDI method, an example of the method disclosed in Hearn.

Applicants submit that insofar as it may be *prima facie* obvious to modify or combine either Milton and/or Hearn et al., the claimed invention provides unexpected advantages. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. § 103 and allowance of all claims.

CONCLUSION

The Applicant believes that all pending claims are in condition for allowance and such action is earnestly requested. If the present amendments and remarks do not place the Application in condition for allowance, the Examiner is encouraged to contact the undersigned directly if there are any issues that can be resolved by telephone with the Applicants representative.

The Commissioner is authorized to charge the fee of \$120, the fee for a one-month extension, to Deposit Account No. 19-2090. The Commissioner is further authorized to charge any other fees associated with this Response and Amendment to Deposit Account No. 19-2090.

Respectfully Submitted,
SHELDON & MAK PC

Date: October 3, 2005

By: 

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